UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,288	11/28/2000	Dale B. Schenk	15270J-004765US	9431

20350 7590 06/21/2006

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 06/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,288	SCHENK ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *90-94,96-98 and 100* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-94,96-98 and 100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5 April 2006 has been entered.

Applicants' Amendment and Response filed 6 February 2006 has been entered. Claim 90 has been amended and claim 95 has been canceled. Claims **90-94**, **96-98**, and **100** are pending and under examination in the current office action.

The Examiner of U.S. Patent Application No. 09/724,288 has changed. In order to expedite the correlation of papers with the application, please direct all future correspondence to Examiner Ballard, Technology Center 1600, Art Unit 1649.

Information Disclosure Statement

A signed and initialed copy of the IDS paper submitted 5 April 2006 is enclosed in this action.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Withdrawn Rejections

In regard to Applicants' request for further clarification of the withdrawal of the species election requirement, the Examiner notes that the timing of the species election withdrawal requirement is regrettable and unfortunate in view of the claims already having been canceled.

The rejection of claims 90-92 and 96-97 under 35 U.S.C. 102(e) as being anticipated by WO 99/60024 by Solomon et al., as stated at p. 4 ¶9 of the 7/12/05 office action, is hereby *withdrawn* in view of Applicants' amendments to the claims. The rejection of claim 99 is rendered moot in view of Applicants' cancellation of the claim.

The rejection of claims 90-94, 96-98 and 100 under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,935,927 to Vitek et al. as evidenced by Benjamini et al., as stated at p. 5-6 of the 7/12/05 office action, is hereby *withdrawn* in view of Applicants' arguments and amendments to the claims. The rejection of claim 95 is rendered moot in view of Applicants' cancellation of the claim.

The rejection of claims 90-94, 96-98 and 100 under 35 U.S.C. 103(a) as set forth at p. 8 ¶12 of the 7/12/05 office action is hereby *withdrawn* in view of Applicants' arguments and amendments to the claims. The rejection of claim 95 is rendered moot in view of Applicants' cancellation of the claim.

The rejection of claims 90-94, 96-98 and 100 under 35 U.S.C. 103(a) as set forth at p. 11 ¶13 of the 7/12/05 office action is hereby *withdrawn* in view of Applicants' arguments and amendments to the claims. The rejection of claim 95 is rendered moot in view of Applicants' cancellation of the claim.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 92 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 92 recites the limitation "phagocytic cells" in the 3rd line of the claim. As claim 92 depends from claim 90, which recites "microglial cells", there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 90-92, 94, 96, and 97 are rejected under 35 U.S.C. 102(a) as being anticipated by Brazil et al. (*J Biol Chem*, 2000; **275**(22): 16941-16947). The Examiner notes the electronic publication date (EDAT) for this reference is listed by PubMed as 5 April 2000 (see attached sheets following the reference), and thus would have been accessible to the public before the printed publication date of June 2000.

Brazil et al. teaches that microglia are capable of internalizing and degrading fibrillar Aβ (fAβ) microaggregrates in culture. Brazil teaches an *in vitro* method to investigate the effects of receptor-mediated uptake of fAβ. In particular, Brazil demonstrates that microglial uptake of fAβ microaggregates pre-incubated with the monoclonal antibody 4G8 (which recognizes residues 17-24 of Aβ; see Methods, p. 16942, 2nd column, which would meet recited limitations of instant claims 92, 94, and 97) is about 1.5-fold greater than that of unmodified fAβ microaggregate preincubated with isotype control IgG (see p. 16943, 2nd column and Figure 2, p. 16944). Brazil notes that the uptake of these fAβ microaggregates pre-incubated with 4G8 (termed IgG-fAβ microaggregates) is mediated by Fc receptors, as competing ligands for Fc receptors were shown to partially block the microglial uptake of IgG-fAβ (see p. 16944, 1st column and Figure 4), thus meeting a recited limitation within instant claim 90. The majority of theses studies were preformed using microscopes to view the uptake of fAβ by microglia (for example, see Figures 2-5), thus meeting a recited limitation of claim 96. Brazil also teaches measurement of radiolabeled fAβ in medium from the microglial cultures over a period of several days (see Methods, p. 16943, 1st column, and Figure

6), thus meeting another recited limitation within claim 90. Accordingly, Brazil anticipates instant claims 90-92, 94, 96 and 97.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 90-94, 96-98 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brazil et al. (*J Biol Chem*, 2000; **275**(22): 16941-16947) in view of DeWitt et al. (*Exp Neurology*, 1998; **149**: 329-340) and WO 99/60024 by Solomon et al., 25 November 1999, and further in view of Johnson-Wood et al. (*Proc Natl Acad Sci USA*, 1997; **94**: 1550-1555; listed on Applicant's IDS filed 9/10/01), Friedland et al. (*Mol Neurobiol*, 1994; **9**: 107-113; listed on Applicant's IDS filed 9/10/01), and Walker et al. (*J Neuropath Exp Neurol*, 1994; **53**(4): 377-383; listed on Applicant's IDS filed 9/10/01).

The teachings of Brazil et al. are discussed *supra*. Briefly, Brazil teaches methods of evaluating the effects of monoclonal anti-Aβ antibody-mediated uptake and degradation of fibrillar Aβ microaggregates *in vitro* and comparing these effects to other receptor-mediated phagocytic processes. However, Brazil does not teach that the amyloid deposits are tissue samples from the brains of Alzheimer's disease patients or from an animal having Alzheimer's pathology, nor does Brazil teach that the monoclonal antibody binds to an epitope within residues 1-7 of Aβ.

DeWitt et al. teach an *in vitro* model in which isolated senile plaque (SP) cores from patients with confirmed Alzheimer's disease (obtained post-mortem) are presented to microglial cells in culture (see Abstract and Methods, p. 330). DeWitt teaches that the microglia phagocytose and degrade the SP cores, which contain Aβ fibrils (see Figure 3), as measured over a period of hours, days and weeks (see p. 334, 1st column and Figure 4). The SP cores presented to microglial cells in this *in vitro* model would thus meet a limitation of instant claims 93 and 100.

Solomon teaches methods for amyloid removal using anti-amyloid antibodies that enhance the cell-mediated immune response to deposits of amyloid and exploit the opsonizing effect of monoclonal antibodies directed to amyloid material, fibrils or its component parts both *in vivo* and *in vitro* (see Summary of the Invention, p. 3). Solomon discloses that the methods are useful for treating diseases such as Alzheimer's disease (see p. 1). In particular, Solomon teaches an *in vitro* neutrophil (a phagocytic cell bearing Fc receptors) binding assay in which neutrophils adhere to human amyloid after the amyloid has been treated with mouse anti-human IgLC monoclonal antibodies, thus demonstrating that the mouse monoclonal antibody can bind to human amyloid as well as attract human neutrophils (see Example 2, p. 18).

The collective teachings of Johnson-Wood et al., Friedland et al., and Walker et al. demonstrate that monoclonal antibodies directed to the N-terminal of Aβ are effective in binding to brain Aβ aggregates both *in vitro* and *in vivo*. For example, Johnson-Wood teaches that the monoclonal antibody 3D6 (which is specific for amino acids 1-5 of Aβ) effectively labeled Aβ plaque burden in brain slices from transgenic PDAPP mice, a

mouse model of Alzheimer's disease (see Figure 4, p. 1553). Similarly, Friedland et al. demonstrate that the monoclonal 10H3 antibody, which was raised against Aβ 1-28, was capable of labeling Aβ plaques in post-mortem brain samples from patients with Alzheimer's disease. And finally, Walker et al. demonstrate that administration of the monoclonal antibody 10D5, which the instant specification reports as having an epitope of Aβ 3-6, to aged monkeys resulted in *in vivo* binding to Aβ deposits in the brains of the monkeys. Taken together, the artisan would recognize that the N-terminus of Aβ must be an accessible epitope on the amyloid deposits to allow the these monoclonal antibodies (mAbs) to bind, and because of this, mAbs directed to the N-terminus of Aβ would thus be important for *in vitro* and *in vivo* diagnostic techniques as well as for potential therapeutic applications (as noted in Walker, p. 382).

Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was filed to modify the *in vitro* method taught by Brazil et al. by substituting brain tissue from AD patients instead of Aβ microaggregates, so as to test the ability of various monoclonal antibodies specific for the N-terminus of Aβ in their ability to stimulate microglial clearance of Aβ. One of ordinary skill in the art would be motivated to combine the above teachings because Solomon teaches that monoclonal antibodies are therapeutically useful as they can bind to amyloid and activate cellular immune clearance mechanisms, such as the attraction of phagocytic cells to amyloid deposits. Thus, there is great therapeutic and commercial benefit to justify adapting the *in vitro* microglial clearance method to screen for antibodies capable of binding to and recruiting microglial cells, thus eliciting a cell-mediated immune response. The skilled

artisan would be motivated to substitute brain tissue samples for prepared fibrillar Aβ because ultimately, the antibodies would be used for therapy and a sample of brain tissue more closely mimics an *in vivo* environment than does a culture comprising aggregated synthetic Aβ. The skilled artisan would also be motivated to focus on monoclonal antibodies that recognize an epitope with Aβ 1-7 because Johnson-Wood et al., Friedland et al. and Walker et al. collectively demonstrate that monoclonal antibodies directed to the N-terminus of Aβ, in particular 3D6 with an epitope of Aβ 1-5 and 10D5 with an epitope of Aβ 3-6, are particularly effective in being able to bind to Aβ aggregates in the brains of patients with Alzheimer's disease and in PDAPP mice. Additionally, Walker notes that *in vivo* labeling using monoclonal antibodies has considerable potential for delivering therapeutic agents that could prevent or reverse Aβ deposition in the brains of patients with Alzheimer's disease (see p. 382, 1st column). The artisan would thus expect that a modified screening assay using brain tissues from AD patients and testing antibody-elicted microglial cell responses would be successful because both Brazil and Solomon show that anti-Aβ antibodies can evoke such phagocytic responses, DeWitt demonstrates that microglia can effectively phagocytose senile plaques from AD patients, and Johnson-Wood, Walker, and Friedland show that N-terminal antibodies can efficiently bind to Aβ aggregates in brain, which is the first step in initiating the cell-mediated immune clearance response. Thus, the above references render obvious instant claims 90-94, 96-98 and 100.

Claims 90-94, 96-98 and 100 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,935,927 to Vitek et al. as evidenced by Benjamini et al. (Immunology, 2nd Edn. 1991, Wiley-Liss, Inc., New York, pp. 73-74, 136-138, 143, 372-373 and 400-401), in view of DeWitt et al. (*Exp Neurology*, 1998; **149**: 329-340) and WO 99/60024 by Solomon et al., 25 November 1999, and further in view of Johnson-Wood et al. (*Proc Natl Acad Sci USA*, 1997; **94**: 1550-1555; listed on Applicant's IDS filed 9/10/01), Friedland et al. (*Mol Neurobiol*, 1994; **9**: 107-113; listed on Applicant's IDS filed 9/10/01), and Walker et al. (*J Neuropath Exp Neurol*, 1994; **53**(4): 377-383; listed on Applicant's IDS filed 9/10/01).

Vitek et al. teach compositions and methods for stimulating amyloid removal in amyloidogenic diseases using advanced glycosylation endproducts (AGEs). The method includes stimulating mechanisms of recognition and removal of AGE-amyloid in an animal to remove the amyloid plaques via scavenger systems. In particular, phagocytic cells such as macrophages and/or microglial cells are treated with an agent capable of causing the phagocytic cells to increase their activity of recognizing and removing AGE-modified amyloid plaques (see column 16, lines 44-52). Vitek also discloses a method for identifying new drugs and corresponding agents capable of treating abnormal amyloid polypeptide aggregation, in one aspect by use of an assay involving AGE-amyloid polypeptide, in particular AGE-Aβ (see column 7, lines 43-48). One such therapeutic agent disclosed by Vitek for inhibition of AGEs are antibodies that bind to and inactivate or mediate clearance of AGE-modified amyloid polypeptides (see column 15, lines 8-10), wherein the antibodies includes monoclonal antibodies (see

column 15, lines 52-59). Opsonization of particles by antibodies and antibody-dependent, cell-mediated cytotoxicty (ADCC) are important mechanisms for clearing the body of potentially harmful substances, such as toxins and bacteria, as well as tumors and other deposits, as evidenced by Benjamini et al. (see in particular p. 73-74). Vitek also discloses an example of an *in vitro* assay used for determining the ability of agents to modulate clearance of AGE-modified insoluble Aβ by incubation with cultured phagocytic cells, such as macrophages, monocytes, or microglia or astroglia primary cells or cell lines (see column 22, lines 54-65).

However, Vitek does not teach a particular *in vitro* assay system to evaluate microglial clearance of tissue samples from the brain of an Alzheimer's disease patient or an animal having Alzheimer's pathology, nor does Vitek teach screening for monoclonal antibodies that bind to an epitope within Aβ 1-7.

The teachings of DeWitt et al. are discussed *supra*. Briefly, DeWitt teaches an *in vitro* model in which isolated senile plaque (SP) cores from patients with confirmed Alzheimer's disease (obtained post-mortem) are presented to microglial cells, which then phagocytose and degrade the SP cores (containing Aβ fibrils), as measured over a period of hours, days and weeks (see p. 334, 1st column and Figure 4). For example, DeWitt measured the number of SP cores (identified immunocytochemically by anti-Aβ antibody, see Methods, p. 330) both extracellularly and intracellularly in regard to microglial cells (see Figure 4). DeWitt noted that the number of extracellular SP cores and the total number of SP cores (an measure of SP core clearance and subsequent breakdown) continually decreased during the culture period, which would meet a recited

limitation of claim 91. The majority of theses studies were preformed using microscopy to evalulate the phagocytosis of Aβ by microglia (see Figure 2, for example). The SP cores presented to microglial cells in this *in vitro* model would thus meet a limitation of instant claims 93 and 100.

The teachings of Solomon are also discussed *supra* and serve to further support therapeutic and analytical teachings of Vitek. In particular, Solomon teaches methods for amyloid removal using anti-amyloid antibodies that enhance the cell-mediated immune response to deposits of amyloid and exploit the opsonizing effect of monoclonal antibodies directed to amyloid material, fibrils or its component parts both *in vivo* and *in vitro*, such as for treatment of Alzheimer's disease. Solomon also describes an *in vitro* ADCC assay used to evaluate recruitment of phagocytic cells to human amyloid deposits treated with mouse anti-human monoclonal antibody (see Example 2, p. 18), thus meeting a recited limitation of claim 92.

The collective teachings of Johnson-Wood et al., Friedland et al., and Walker et al. are discussed *supra* and suggest not only that the N-terminus of Aβ is an epitope accessible for binding of antibodies on the surface of amyloid plaques in brains of patients with AD and in animal models of AD, but also demonstrate not that monoclonal antibodies directed to the N-terminal of Aβ are effective in binding to brain Aβ aggregates both *in vitro* and *in vivo*. Thus, Walker proposes that monoclonal antibodies such as 10D5 (and 3D6, both of which recognized epitopes within Aβ 1-7), are particularly valuable for *in vitro* and *in vivo* diagnostic techniques as well as for potential therapeutic applications (as noted in Walker, p. 382).

Accordingly, it would have been obvious to the person of ordinary skill in the art at the time the invention was filed to modify the drug screening method taught by Vitek by substituting brain tissue from AD patients (as taught by DeWitt) for Aβ aggregates, so as to test the ability of monoclonal antibodies specific for the N-terminus of Aβ in their ability to stimulate microglial clearance of Aβ. One of ordinary skill in the art would be motivated to combine the above teachings because both Vitek and Solomon teach that monoclonal antibodies are therapeutically useful as they can bind to amyloid and activate cellular immune clearance mechanisms, such as the attraction of phagocytic cells to amyloid deposits. Thus, there is great therapeutic and commercial benefit to justify adapting the *in vitro* phagocytic clearance method to screen for antibodies capable of binding to and recruiting microglial cells (the resident macrophages of the brain), thus eliciting a cell-mediated clearance response of amyloid deposits in brain tissue. The skilled artisan would be motivated to substitute brain tissue samples for prepared fibrillar Aβ because ultimately, the antibodies would be used for therapy and a sample of brain tissue more closely mimics an *in vivo* environment than does a culture comprising aggregated synthetic Aβ. The skilled artisan would also be motivated to focus on monoclonal antibodies that recognize an epitope with Aβ 1-7 because Johnson-Wood et al., Friedland et al. and Walker et al. collectively demonstrate that monoclonal antibodies directed to the N-terminus of Aβ, in particular 3D6 with an epitope of Aβ 1-5 and 10D5 with an epitope of Aβ 3-6, are particularly effective in being able to bind to Aβ aggregates in the brains of patients with Alzheimer's disease and in PDAPP mice. Additionally, Walker notes that *in vivo* labeling using monoclonal

antibodies has considerable potential for delivering therapeutic agents that could prevent or reverse Aβ deposition in the brains of patients with Alzheimer's disease (see p. 382, 1st column). The artisan would thus expect that a modified screening assay using brain tissues from AD patients and testing antibody-elicted microglial cell responses would be successful because Solomon shows that monoclonal antibodies can evoke such phagocytic responses, DeWitt demonstrates that microglia can effectively phagocytose senile plaques from AD patients, and Johnson-Wood, Walker, and Friedland show that N-terminal monoclonal antibodies can efficiently bind to Aβ aggregates in brain, which is the first step in initiating the cell-mediated immune clearance response. Thus, the above references render obvious instant claims 90-94, 96-98 and 100.

Conclusion

All claims are rejected.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
Art Unit 1649
June 15, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER